

Clinical pharmacological studies of amoxycillin: effect of probenecid

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SUMMARY In a study of eight, healthy, adult volunteers given 3 g amoxycillin with or without 1 g probenecid, significantly higher peak plasma levels of amoxycillin were recorded in the presence ($34.96 \mu\text{g/ml}$) of probenecid than in its absence ($22.72 \mu\text{g/ml}$). When plasma levels were plotted against time the mean area under the curve was significantly greater for subjects given probenecid than for those given amoxycillin alone. These findings suggest that 3 g amoxycillin plus 1 g probenecid provide better bioavailability than 3 g amoxycillin alone. The plasma levels obtained were several times higher than the minimum inhibitory concentrations (MICs) of most strains of gonococci. Plasma levels in excess of the MICs for most strains were maintained for eight hours with both regimens, but the higher levels in the presence of probenecid support the better clinical results previously reported with this regimen.

Introduction

Amoxycillin is a semisynthetic penicillin similar in chemical structure and spectrum of activity to ampicillin (Sutherland *et al.*, 1972) but is much better absorbed after oral administration (Croydon and Sutherland, 1971; Gordon *et al.*, 1972). Probenecid competes with penicillins and other organic anions for renal secretion, resulting in higher plasma levels of penicillin when they are administered together (Burnell and Kirby, 1951; Vitti *et al.*, 1974). Probenecid has been used together with ampicillin and amoxycillin for single-dose therapy for gonorrhoea (Karney *et al.*, 1974; Thin *et al.*, 1977). To investigate this further, plasma levels achieved after a dosage of 3 g amoxycillin with or without concurrent administration of 1 g probenecid were estimated in healthy volunteers. In view of the uncertain fasting state of patients receiving the antibiotic therapy for gonorrhoea and the small effect of food on plasma levels of amoxycillin (Neu and Winshell, 1971) the kinetic study was carried out in non-fasting healthy volunteers.

Materials and methods

The clinical pharmacological studies were conducted in eight healthy adult volunteers (age 22-26 years, weight 60-80 kg), all of whom gave informed consent. All subjects were shown by medical examination to be in good physical condition with normal blood and urine laboratory values. No subject had a history of allergic reactions to penicillins or cephalosporins. No other medication was taken by the subjects during the study.

Four subjects received 3 g ($1 \text{ g} \times 3$) amoxycillin with 1 g probenecid, and the other four received the same medication without probenecid. One week later the subjects were given the treatment they had not received during the first week. The treatment was administered orally with 100 ml water at least two hours after a standard breakfast of fruit juice and toast, and no food was allowed thereafter for four hours.

Blood samples were collected just before (zero hour) and at $\frac{1}{2}$, 1, $1\frac{1}{2}$, 2, 3, 5, 6, and 8 hours after the antibiotic administration. Plasma samples obtained were kept frozen at -20°C until assayed by a fluorimetric assay (Barbhaiya *et al.*, 1977). A plot of the time course versus plasma levels of amoxycillin with or without probenecid was obtained for each subject, and from this the area under the curve (AUC) between zero and eight hours was calculated.

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The AUC was taken as a measure of relative absorption of amoxycillin in the absence and presence of probenecid. Paired *t* tests were used to assess the significance of within-subject differences and the optimal concentration/time curves were calculated for each subject using a least-squares, fitting technique.

Results

Plasma concentrations of amoxycillin achieved in each subject after administration of a single oral dose of 3 g amoxycillin with or without concurrent administration of 1 g probenecid are presented in Table 1. In the absence and presence of probenecid mean peak plasma amoxycillin levels were achieved at three hours and ranged from one to four hours. The mean peak plasma level for amoxycillin was significantly higher when probenecid was administered ($34.96 \mu\text{g/ml}$) than that achieved without administration of probenecid ($22.72 \mu\text{g/ml}$) ($t = 3.62$; $P < 0.01$). The peak plasma concentrations ranged from 23.20 – $62.00 \mu\text{g/ml}$ in the presence of probenecid and from 15.34 – $32.46 \mu\text{g/ml}$ in its absence (Table 1).

The mean area under the curve was significantly higher in the presence of probenecid than that obtained in its absence in each of the eight subjects (paired *t* test = 6.13 ; $P < 0.001$). The mean AUC without probenecid was 128.93 ± 6.13 and with probenecid 208.55 ± 9.22 . The AUC ranged between 170.84 – 233.29 and 115.65 – 165.66 in the presence and absence of probenecid respectively (Table 2).

Table 2 Area under the concentration/time curve for amoxycillin with and without probenecid

Subject no.	Area under concentration/time curve for amoxycillin	
	With probenecid	Without probenecid
1	233.29	115.65
2	170.84	165.66
3	242.24	130.63
4	222.14	139.94
5	225.90	109.69
6	179.69	114.84
7	199.74	139.99
8	199.64	115.29
Mean \pm SEM	208.55 ± 9.22	128.93 ± 6.72

Discussion

Several studies have compared the clinical pharmacology of amoxycillin and ampicillin after oral administration and have uniformly demonstrated significantly better absorption levels of amoxycillin (Gordon *et al.*, 1972; Sutherland *et al.*, 1972). The plasma levels of these antibiotics are considerably raised in the presence of probenecid. The present study shows that 3 g amoxycillin achieves higher plasma levels in the absence of probenecid than those reported for 3.5 g ampicillin with 1 g probenecid and equivalent peak levels to those reported for 2 g amoxycillin with 0.5 g probenecid (Vitti *et al.*, 1974). The mean plasma levels obtained in eight subjects given 3 g amoxycillin

Table 1 Concentration of amoxycillin in plasma of non-fasting volunteers after oral administration

Subject no. and regimen	Antibiotic concentration ($\mu\text{g/ml}$) at given time intervals (hours)							
	$\frac{1}{2}$	1	$1\frac{1}{2}$	2	3	4	6	8
Amoxycillin 3 g								
1	6.47	9.96	15.19	13.45	19.72	18.68	8.56	4.50
2	3.15	8.20	18.5	29.32	32.46	27.60	11.00	5.45
3	12.47	23.11	30.52	28.42	26.36	19.40	6.00	4.30
4	1.46	6.34	15.80	16.90	28.86	23.16	12.72	4.60
5	1.47	5.05	11.23	12.60	15.34	13.25	10.80	6.97
6	3.70	10.80	12.90	16.74	18.84	20.23	9.42	3.00
7	3.80	9.40	16.80	19.50	24.76	21.20	12.30	5.30
8	2.90	8.30	14.19	16.15	20.40	18.67	9.00	4.60
Mean \pm SEM	4.46 ± 1.2	10.45 ± 1.96	16.90 ± 2.10	19.13 ± 2.25	22.72 ± 1.57	20.27 ± 1.45	9.98 ± 0.77	4.46 ± 0.59
Amoxycillin 3 g and probenecid 1 g								
1	2.10	12.20	19.20	23.40	34.53	32.45	20.54	14.00
2	8.68	30.14	35.92	43.00	34.40	22.11	12.17	5.00
3	8.00	29.50	49.00	62.00	51.60	32.00	14.95	7.50
4	2.30	5.80	9.40	13.95	25.50	28.95	18.83	13.95
5	2.65	6.62	12.40	14.50	32.00	33.50	18.50	13.50
6	6.71	12.95	18.45	22.41	26.68	23.20	16.50	10.00
7	8.50	20.22	31.72	36.21	38.40	26.25	14.60	8.70
8	4.28	13.92	19.79	28.60	36.62	28.92	16.12	9.79
Mean \pm SEM	5.4 ± 1.0	16.40 ± 3.32	24.49 ± 4.69	30.51 ± 5.72	34.96 ± 2.60	28.42 ± 1.50	16.50 ± 0.97	10.31 ± 1.17

and 1 g probenecid were considerably higher than those achieved without concurrent administration of probenecid. After administration of 500 mg and 1000 mg amoxycillin, peak levels of 7.9 µg/ml and 12.0 µg/ml respectively after one hour have been reported (Verbist, 1974; Spyker *et al.*, 1977). Vitti *et al.* (1974), however, reported 23.1 µg/ml and 21.4 µg/ml peak plasma levels at three hours after administration of 2 g amoxycillin with 0.5 g probenecid and 3 g amoxycillin alone respectively. In the same study the plasma concentration at eight hours with 2 g amoxycillin and 0.5 g probenecid combined was 3.8 µg/ml whereas that of 3 g amoxycillin was 1.8 µg/ml. Probenecid, therefore, appeared to be blocking renal excretion and prolonging plasma levels. The mean peak plasma levels observed during the present investigation (22.7 µg/ml at three hours with 3 g amoxycillin without probenecid) is in close agreement with the findings of Vitti *et al.* (1974). In the present study, however, a mean peak level of 4.46 µg/ml amoxycillin was observed at eight hours for the dosage regimen without probenecid compared with that of 1.80 µg/ml reported by the same author. Significantly higher peak plasma levels and area under the curves obtained for 3 g amoxycillin with 1 g probenecid than those for 3 g amoxycillin alone suggest better bioavailability with the former dosage regimen. The plasma levels were several times higher than the MIC values of most strains of gonococci sensitive to amoxycillin.

A correlation between low plasma levels, relative penicillin resistance, and increased failure rates in the treatment of gonorrhoea with previously adequate antibiotic regimens has been well documented (Eisenstein, 1977). Probenecid was introduced, therefore, to achieve a cure rate of over 95%. Eagle *et al.* (1948) emphasised the importance of the duration of effective penicillin bactericidal levels, based on the fact that the cells need to be growing in order to be affected. Eriksson (1971) reported that it took at least five, and as long as 12, hours of bactericidal concentrations of ampicillin to cure

gonorrhoea. Thus, the duration of antibiotic levels as well as their magnitude are important. The success of the recently conducted clinical trial for the treatment of gonorrhoea using a single oral dose of 3 g amoxycillin with 1 g probenecid (Thin *et al.*, 1977) may be attributed, at least in part, to the higher and persistent plasma levels observed with such a dosage regimen.

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